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(54) Title: LIGNAN COMPLEXES

(57) Abstract: This invention concerns an inclusion complex of a lignan or lignan ester with a cyclodextrin. Furthermore, the invention concerns food products, dietary supplements or pharmaceutical compositions comprising said complex.

WO 2004/020474 A1

LIGNAN COMPLEXES

FIELD OF THE INVENTION

- 5 This invention relates to cyclodextrin complexes of lignans or lignan esters, and to the use of such complexes in various food compositions, dietary supplement products or pharmaceuticals.

BACKGROUND OF THE INVENTION

10

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference.

- 15 Cyclodextrins and their use:

- Cyclodextrins (CDs) are a group of cyclic oligosaccharides which have been shown to improve pharmaceutical properties of lipophilic drugs by forming inclusion complexes (Frömming K-H, Szejtli J, Cyclodextrins in pharmacy, 20 Kluwer Academic Publishers, Dordrecht, 1994). Cyclodextrins are cone-shaped molecules with two openings. The cavity of the molecule is hydrophobic while the surface of the molecule is hydrophilic. An inclusion complex is formed when the lipophilic guest molecule, or part of it, enters into the apolar cavity of the cyclodextrin. Inclusion complex formation is 25 mainly based on hydrophobic interactions between drug and cyclodextrin, and no covalent bonds are formed during the complexation.

- Cyclodextrins are either natural cyclodextrins or derivatives thereof (Thompson D: Cyclodextrins-enabling excipients: their present and future use 30 in pharmaceuticals. Crit. Rev. Ther. Drug Carrier Syst. 14: 1 – 104, 1997).

Natural cyclodextrins are enzymatic degradation products of starch, formed from six (α -cyclodextrin or α -CD), seven (β -cyclodextrin or β -CD) or eight (γ -cyclodextrin or γ -CD) glucopyranose units. Modified cyclodextrins, such as methyl-, hydroxyalkyl-, and sulfoalkylether derivatives of natural
5 cyclodextrins, have been developed to increase the aqueous solubility and pharmaceutical usefulness of natural cyclodextrins. So far, the most commonly studied cyclodextrin derivative in drug development is hydroxypropyl- β -cyclodextrin (HP- β -CD).

- 10 Cyclodextrins have traditionally been used to increase the aqueous solubility and chemical/physical stability of lipophilic drugs (Loftsson T, Brewster M E: Pharmaceutical applications of cyclodextrins. 1. drug solubilization and stabilization. J. Pharm. Sci. 85: 1017 – 1025, 1996). However, the complexation of a drug with cyclodextrins may also increase its
15 bioavailability or decrease side-effects (Rajewski R A, Stella V J: Pharmaceutical applications of cyclodextrins 2. in vivo drug delivery. J. Pharm. Sci. 85: 1142 – 1169, 1996). In addition (as with food and cosmetics preparations), cyclodextrins have also been studied in drug formulations to mask the unpleasant taste or odour of drugs (Frömming and Szejtli 1994).
20 Until now, the utilization of cyclodextrins has been limited to relative small molecules, but cyclodextrins are also useful with macromolecules (e.g., proteins and peptides) which will extend their utilization in the future (Irie T, Uekama K: Cyclodextrins in peptide and protein delivery. Adv. Drug Del. Rev. 36: 101 – 123, 1999).

25

A problem with natural β -CD is that it causes nephrotoxicity after parenteral administration (Irie T, Uekama K: Pharmaceutical applications of cyclodextrins . III. Toxicological issues and safety evaluation. J. Pharm. Sci. 86:147 – 162, 1997). However, in oral administration β -CD does not show

any toxicity due to its minor absorption from the gastrointestinal tract.

Similarly, the other natural cyclodextrins and derivatives thereof do not absorb from the gastrointestinal tract due to the bulky and hydrophilic character of cyclodextrin molecules. In the gastrointestinal tract,

5 cyclodextrins (except for natural γ -CD) are remarkably resistant to the usual starch hydrolysing enzymes. The cyclodextrins cannot be hydrolyzed by β -amylase and they are hydrolysed by α -amylase at a very low rate. The fundamental physiological difference between cyclodextrins and starch is that the metabolism of cyclodextrins takes place in the colon while starch is
10 metabolized in the small intestine. The metabolites of cyclodextrins (maltose, glucose, acyclic maltodextrins) are rapidly metabolized further and finally excreted as CO_2 and H_2O . In general, introduction of substituents on the hydroxyl groups slows down enzymatic hydrolysis of the cyclodextrin by lowering its enzyme affinity.

15

Lignans:

Lignans are phenolic compounds widely distributed in plants. They can be found in different parts (roots, leafs, stem, seeds, fruits) but mainly in small
20 amounts. In many sources (seeds, fruits), lignans are found as glycosidic conjugates associated with fiber component of plants. The most common dietary source of mammalian lignan precursors are unrefined grain products. The highest concentrations in edible plants have been found in flaxseed, followed by unrefined grain products, particularly rye.

25

Considerable amounts of lignans are also found in coniferous trees. The type of lignans differs among different tree species and the amounts of lignans varies between different parts of the tree. The typical lignans in heartwood of Norway spruce (*Picea abies*) are hydroxymatairesinol (HMR), alpha-
30 conidendrin, alpha-conidendric acid, matairesinol, isolariciresinol,

secoisolariciresinol, liovil, picearesinol, lariciresinol and pinoresinol (Ekman R: Distribution of lignans in Norway spruce. Acta Academiae Aboensis, Ser B, 39:1-6, 1979). The far most abundant single component of lignans in spruce is HMR, about 60 per cent of total lignans, which occurs mainly in non-glycosylated form.

Plant lignans such as HMR, matairesinol, lariciresinol and secoisolariciresinol, are converted by gut microflora to mammalian lignans, enterolactone or enterodiol. The mammalian lignans can also be manufactured synthetically (MB Groen and J Leemhuis, Tetrahedron Letters 21, 5043, 1980).

Lignans are known to possess beneficial effects on human health. The health benefits obtained with lignan rich diet are, for example, decreased risk for various cancers and cardiovascular diseases (Adlercreutz (1998) Phytoestrogens and human health, In: Reproductive and Developmental Toxicology (edited by Korach, K.). pp. 299-371, Marcel & Dekker, NY.).

Lignans, such as HMR, WO 00/59946, have also been reported to inhibit lipid peroxidation and LDL oxidation and thus be useful as antioxidants.

Also lignans other than HMR have powerful antioxidant and anti-inflammatory potential. The antioxidant action involves all the major free radicals such as superoxide anions and peroxy radicals (K Prasad: Antioxidant activity of secoisolariciresinol diglucoside-derived metabolites, secoisolariciresinol, enterodiol and enterolactone. Int J Angiology 9:220-225 (2000)).

There is evidence to suggest that lignans may also prevent skin cancers (Thompson L.U. (1993): Potential health benefits and problems associated with antinutrients in foods. Food Res. Int. 26, 131-149).

- 5 While literature discloses several different chemical substances that can be complexed with different cyclodextrins, the cyclodextrin complexes of lignans or their derivatives have not been reported so far.

OBJECTS AND SUMMARY OF THE INVENTION

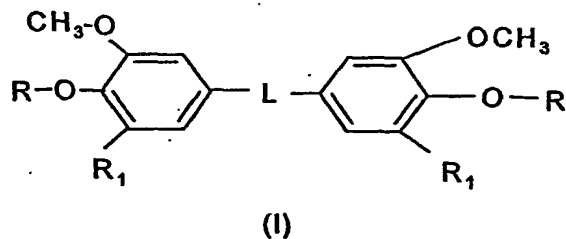
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There is a great need to provide novel improved formulations containing lignans or derivatives thereof for use as various kinds of food products, dietary supplements or pharmaceutical use in which formulations the solubility, bioavailability and stability of the active compound is satisfactory.

- 15 Furthermore, masking of possible unpleasant taste or odour of the active compounds is also important.

Thus, according to one aspect, this invention concerns an inclusion complex of a lignan or lignan ester with a cyclodextrin, wherein the lignan or lignan ester is a compound of formula (I)

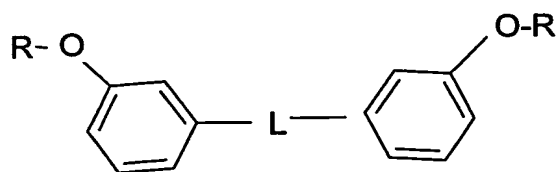
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25

or formula (II)

30



(II)

- 5 wherein L is a lignan skeleton which optionally includes a bridge forming a ring with one of the phenyl groups in the formulae (I) or (II); R₁ is H or methoxy,
and R is H, methyl, R'-CO- or R'-SO₂-, wherein
R' is a C₁ to C₂₂ alkyl, alkenyl, arylalkyl, aralkenyl, or an aromatic group, and
10 R' is unsubstituted or substituted with one or more hydroxy groups and/or one or more carboxyl groups, an oxo group or an amino group,
or a geometric isomer or a stereoisomer thereof, provided that R is methyl only in a single R-O- substituent in a compound of formula (I) where L is a skeleton of the lignan arctigenin.

15

According to another aspect, this invention concerns a food product comprising said inclusion complex and a foodstuff.

- 20 According to a third aspect, the invention concerns a dietary supplement composition comprising said inclusion complex and an acceptable carrier.

According to a fourth aspect, the invention concerns a pharmaceutical composition comprising said inclusion complex and an acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an example of B-type phase-solubility diagram, where the concentration of the active compound is shown on the y-axis and cyclodextrin concentration on the x-axis.

Figure 2 shows a phase-solubility diagram of hydroxymatairesinol (HMR) with γ -cyclodextrin (γ -CD)

Figure 3 shows a phase-solubility diagram of hydroxymatairesinol diacetate (HMRdiAc) with γ -cyclodextrin

Figure 4 shows a phase-solubility diagram of matairesinol (MR) with γ -cyclodextrin

Figure 5 shows a phase-solubility diagram of matairesinol dibutyrate (MRdiBu) with γ -cyclodextrin

Figure 6 shows a phase-solubility diagram of secoisolariciresinol (SECO) with γ -cyclodextrin

Figure 7 shows a phase-solubility diagram of hydroxymatairesinol (HMR) with hydroxypropyl- β -cyclodextrin (HP- β -CD)

Figure 8 shows the degradation of hydroxymatairesinol as function of time in the presence (squares) or absence (triangles) of 2 % γ -cyclodextrin.

DETAILED DESCRIPTION OF THE INVENTION

Preferred cyclodextrins:

- 5 Although any natural cyclodextrin or derivative thereof could be employed in this invention, natural α -, β - or γ -cyclodextrins are preferred. Particularly preferred is γ -cyclodextrin. Preferred derivatives are methyl-, hydroxyalkyl- and sulfoalkylether derivatives of natural cyclodextrins. An especially preferred cyclodextrin derivative is hydroxypropyl- β -cyclodextrin.

10

Preferred lignans and lignan esters:

- As can be seen in Scheme 1, lignans bear typically two phenyl groups, which in turn are substituted with at least a hydroxy group. An exception is the
15 lignan arctigenin in which one of the phenolic hydroxyl groups is replaced by methoxy. Most of the lignans of formula (I) have disubstituted phenyl groups, i.e. R_1 is H. An exception is the rye lignan syringaresinol in which R_1 is methoxy. The lignan skeleton L in the formulae (I) and (II) stands for the part of the lignan molecule bearing such phenyl groups. In certain lignans such as
20 isolariciresinol and conidendrin, the skeleton L includes a bridge which forms a ring with one of the phenyl groups in the formulae. As further can be seen, many of the lignans have also one or more hydroxy groups in the skeleton L.

- Preferred lignans are lignans according to formula (I) which are
25 hydroxymatairesinol, matairesinol, lariciresinol, secoisolariciresinol, isolariciresinol, oxomatairesinol, alpha-conidendrin, pinioresinol, liovil, picearesinol, arctigenin, syringaresinol or nortrachelogenin, or lignans of formula (II), which are enterolactone or enterodiols.

Especially preferred lignans are hydroxymatairesinol, matairesinol, lariciresinol, secoisolariciresinol and isolariciresinol and their geometric isomers and stereoisomers.

5 "Esters" of lignans shall mean either phenolic esters (where the hydroxy groups in the phenol are esterified) or esters where hydroxy substituents in the lignan skeleton are esterified. Many esters of the latter kind are disclosed in the art. Certain phenolic lignan esters are also known in the art, namely the dibenzoate and the p-nitrodibenzoate of matairesinol; enterolactone diacetate;
10 monoacetate, triacetate, p-hydroxymonobenzoate, and p-hydroxy-m-methoxymonobenzoate of hydroxymatairesinol; and tetraacetate and tetrabenzoate of secoisolariciresinol. Other phenolic diesters of lignans defined by formulas (I) or (II) have recently been disclosed in a patent application.

15

The ester is preferably a phenolic ester, in particular a phenolic diester.

Preferable diphenolic lignan esters are, for example, esters of mono- or dicarboxylic fatty acids, hydroxy acids and sulfonic acids. As examples of
20 suitable dicarboxylic acid lignan esters can be mentioned succinates, glutarates, and malonic acid esters. Lactic acid esters are examples of esters with hydroxysubstituted acids. Tartaric acid and citric acid esters are examples of esters of acids with several carboxylic groups and one or more hydroxy groups.

25

Preparation of the inclusion complex:

The cyclodextrin inclusion complex of the lignans or lignan esters are preferably prepared by adding the compound to the cyclodextrin in an acetate
30 buffer at pH 5. The complex formed can be precipitated and isolated.

However, the solid inclusion complex of lignan and cyclodextrin can also be prepared simply by freeze-drying or spray-drying the solution. In addition, methods such as kneading, grinding, neutralization and so-called slurry methods have been used to prepare solid inclusion complexes.

5

The inclusion complex according to this invention can be provided in the form of a pharmaceutical preparation, dietary supplement, or a food product.

The pharmaceutical preparation is preferably an oral formulation. The required amount of the active compound or mixture of compounds will vary with the compound and the particular condition to be prevented. A typical dose ranges from about 1 to about 2000 mg (calculated as lignan) per day and adult person, preferably 10 to 600 mg per day and adult person. Typical dosage forms include, but are not limited to, oral dosage forms such as powders, granules, capsules, tablets, caplets, lozenges, liquids, elixirs, emulsions and suspensions. All such dosage forms may include conventional carriers, diluents, excipients, binders and additives known to those skilled in the medicinal and pharmaceutical arts.

The carriers typically employed for the pharmaceutical composition or dietary supplement composition may be solid or liquid. Thus, for example, solid carriers include polysaccharides such as lactose, sucrose, gelatin, agar, while liquid carriers include aqueous solutions of salts, polysaccharides, complexing agents, surfactants, syrups, vegetable oils such as peanut oil or olive oil, and certain alcohols. However, any acceptable solid or liquid carrier can be used in the pharmaceutical preparation or other dietary or nutrition formula to be administered according to this invention.

A typical food product, suitable for use in the methods according to this invention, is especially a functional food, a nutritional supplement, a nutrient,

a pharmafood, a nutraceutical, a clinical nutritional product, a health food, a designer food or any food product. The term food product shall also be understood to cover groceries and foodstuffs such as flour, other ingredients, certain liquids etc.. A suitable concentration of the active compound in the food product is, for example, 1 to 1000 mg of active compound per 100 g of food product, preferably about 10 to 100 mg of active compound per 100 g of food product.

The invention will be illuminated by the following non-restrictive
Experimental Section.

EXPERIMENTAL SECTION

Materials and methods

Chemicals

The lignans and lignan esters (hydroxymatairesinol (HMR), matairesinol (MR), hydroxymatairesinol diacetate (HMRdiAc), matairesinol dibutyrate (MRdiBu) and secoisolariciresinol (SECO)) were received from Hormos Nutraceutical Ltd. and natural γ -CD and HP- β -CD was purchased from Wacker-Chemie GmbH (Burghausen, Germany). All other chemicals used were of analytical grade.

Apparatus

The samples from the solubility and stability studies were analysed by using the HPLC system which consist of the UV-detector (L-7400), interface module (D-7000), pump (L-7100) and autosampler (L-7250, Merck Hitachi, Japan). Purospher[®] reversed phase column (RP-18e, 5 μ m, 125 x 4 mm) was used in all chromatographic separations.

Solubility studies

The complexation of lignans and lignan esters with γ -CD was studied by using the phase-solubility method of Higuchi and Connors (Higuchi T, 5 Connors K.A. Phase-solubility techniques. Adv. Anal. Chem. Instr. 4: 117-212, 1965). An excess amount of lignan or lignan ester was added to acetate buffer (0.16 M; pH 5.0; ionic strength 0.5) containing various concentrations of γ -CD (0 – 10 %). The suspensions were shaken in the dark (25 °C) for 24 hour and the pH of the suspensions were monitored during the equilibration. 10 The pH of suspensions was adjusted to 5.0 with HCl or NaOH if necessary. After equilibration, the suspensions were filtered through 0.45 μ m membrane filters and analysed by HPLC.

The phase solubility studies with HMR was also performed with HP- β -CD (0 15 – 10 %). In the case of HP- β -CD the equilibration time was 72 hours.

Stability studies

The chemical stability of HMR was studied in acetate buffer (0.16 M; pH 5.0; 20 ionic strength 0.5) in the presence and absence of 2 % γ -CD at 30 °C. All the solutions were prepared by dissolving 1.5 – 2.0 mg of HMR into 20 ml of the solutions mentioned above, and the concentration of the remaining HMR was determined at appropriate intervals by HPLC. The pseudo-first order rate constant for overall degradation of HMR was determined from the slopes of 25 the linear semilogarithmic plots of remaining HMR versus time. The results of the stability studies were calculated as an average of three determinations.

Results

Figure 1 shows an example of the B-type phase-solubility diagram. In B-type phase-solubility diagram the concentration of the active compound, e.g. the complexed drug, first increases with increasing cyclodextrin concentration due to complexation of the active compound with the cyclodextrin molecules. However, after initial improvement in compound solubility, the maximum solubility of the complex is achieved and no further improvement is reached with increasing cyclodextrin concentration (highest part of the diagram). At a certain cyclodextrin concentration, the solubility of the compound begins to decrease in the B-type phase-solubility diagram, because at high cyclodextrin concentrations the compound forms lower solubility complexes with cyclodextrins. The B-type phase-solubility behaviour is typical for natural cyclodextrins and has been described earlier e.g. with steroid hormones (Uekama K, Fujinaga T, Hirayama F, Otagiri M, Yamasaki M. Inclusion complexation of steroid hormones with cyclodextrins in water and in solid phase. *Int. J. Pharm.* 10: 1 – 15, 1982).

20 Solubility studies

Table 1 shows the effect of γ -CD on the aqueous solubility of the selected lignans and lignan esters at pH 5.0. The same data are also shown in figures 2-6 showing the phase-solubility data in graphical form. Figures 2-6 show that all the lignans and lignan esters studied form B-type phase solubility diagram with γ -CD.

Table 1. The effect of γ -CD on the aqueous solubility of lignans (0.16 M acetate buffer; pH 5.0; $\mu = 0.5$, 25 °C; equilibration time 24 hours)

	γ -CD (g/100ml)	HMR (mg/ml)	HMRdiAc (mg/ml)	MR (mg/ml)	MRdiBu (μ g/ml)	SECO (mg/ml)
5	0	6.70	0.75	0.49	-*	0.70
	1	8.85	1.46	2.27	-*	1.74
10	2	10.80	2.07	1.69	0.87	2.02
	5	5.50	0.94	1.47	1.21	1.78
	10	2.21	0.16	0.41	0.84	0.39

*= concentration is under the detection limit of the HPLC method employed.

15

The complexation of HMR was also studied with HP- β -CD which is the most commonly used cyclodextrin derivative in drug development at present. The results (Table 2) show that HP- β -CD forms an inclusion complex with HMR and increases aqueous solubility of HMR. The same data are also shown in Figure 7.

20

Table 2. The effect of HP- β -CD on aqueous solubility of HMR (0.16 M acetate buffer; pH 5.0; $\mu = 0.5$; 25 °C; equilibration time 72 hours)

	HP- β -CD concentration (g/100 ml)	Aqueous solubility of HMR (mg/ml)
25	0	14.56
30	1	14.90
	2	14.94
	5	20.16
	10	26.83

35

Stability studies

The overall degradation of HMR followed first-order kinetics in the presence and absence of 2 % γ -CD at pH 5.0 (Figure 8). Table 3 shows the first-order rate constants, half-lives ($t_{1/2}$) and shelf-lives ($t_{90\%}$) for the chemical degradation of HMR.

40

The stability studies showed that 2 % of γ -CD increases the chemical stability of HMR about 12-fold at pH 5.0.

- 5 Table 3. First-order rate constants (k_{obs}), half-lives ($t_{1/2}$) and shelf-lives ($t_{90\%}$) for chemical degradation of HM-3000 at pH 5.0 (30 °C).

Vehicle	k_{obs} (h^{-1})	$t_{1/2}$ (h)	$t_{90\%}$ (h)
10 0.16 M Acetate buffer (pH 5.0)			
- Without γ -CD	6.91×10^{-4}	1003	152
- With 2% γ -CD	5.71×10^{-5}	12134	1845

15

Conclusions

The results show that lignans and lignan esters form complexes with natural γ -cyclodextrin. With all the lignans and lignan esters studied, γ -CD complexation increased the aqueous solubility of the compounds at low γ -CD concentrations. However, at high γ -CD concentrations lignans and lignan esters form higher order complexes with natural γ -CD which results in decreased aqueous solubility (B-type phase-solubility behaviour). The main advantage of the B-type phase-solubility behaviour is the simple and effective preparation of the pure inclusion complexes by precipitation. Usually CD-containing products are the mixtures of non-complexed molecules of the active agent, complexed molecules of the active agent, and "empty" CD molecules. However, the B-type phase solubility behaviour allows the preparation of pure cyclodextrin complexes of the active agent, i.e. no free cyclodextrin molecules and molecules of the active agent are present in the product.

The present study also shows that the complexation of HMR with γ -CD significantly increases the aqueous stability of HMR. The present study was

carried out at 2 % γ -CD concentration where HMR has the best solubility and the stoichiometry of the complex is most probably 1:1. Thus, it might be possible to improve the aqueous stability of HMR further by increasing the CD concentration which also changes the stoichiometry of the complex.

5

In addition, the present study shows that HP- β -CD can be used to improve the aqueous solubility of HMR.

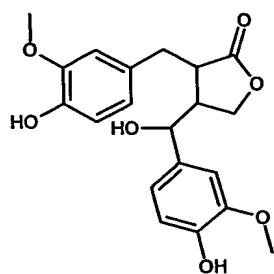
The present study shows that the solubility of HMR without CDs is highly
10 dependent on the equilibration time. Thus, it is important to point out that one of the major benefits of cyclodextrine complexation of lignans or lignan esters may also be the significant improvement the dissolution rate of the compounds, because cyclodextrins have been shown to increase the dissolution rate of lipophilic compounds in various applications.

15

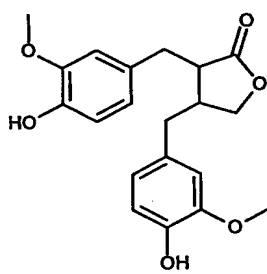
It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the expert skilled in the field that other embodiments exist and do not depart from the spirit of the invention.

20 Thus, the described embodiments are illustrative and should not be construed as restrictive.

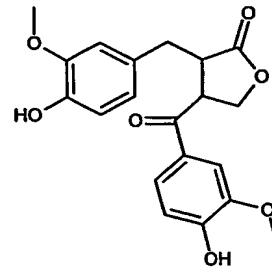
Scheme 1



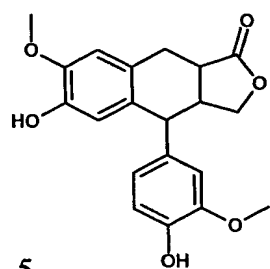
Hydroxymatairesinol



Matairesinol

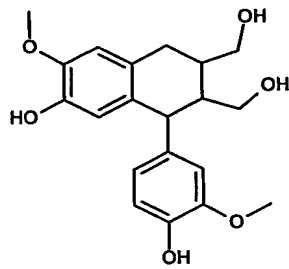


Oxomatairesinol

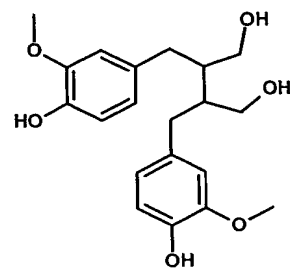


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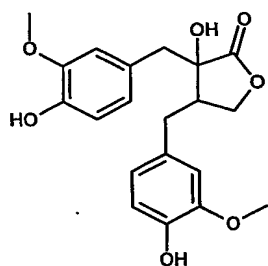
Conidendrin



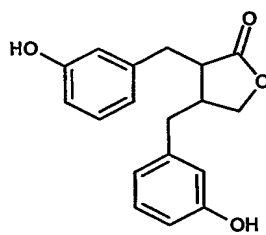
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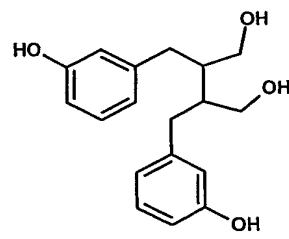
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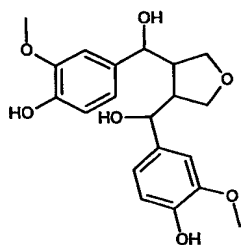


Enterolactone

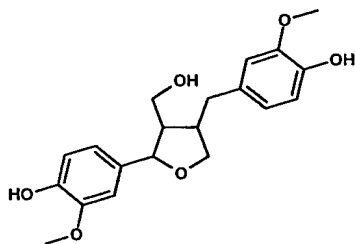


Enterodiol

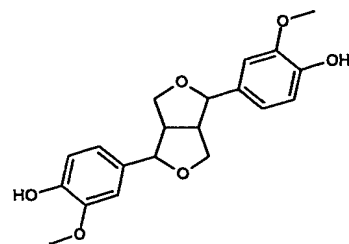
10



Liovil



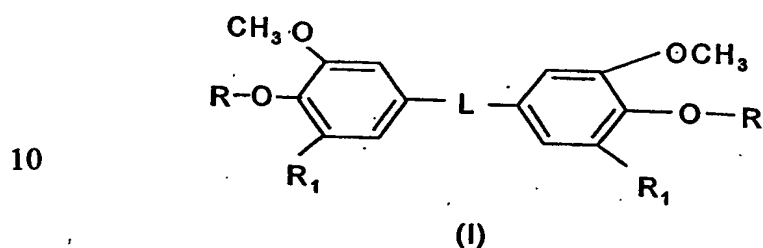
Lariciresinol



Pinoresinol

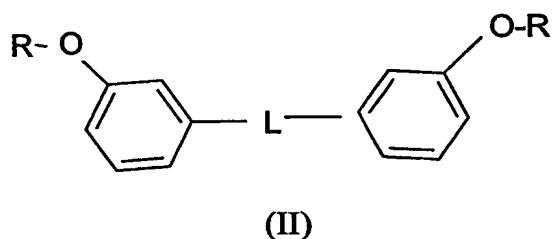
CLAIMS

1. An inclusion complex of a lignan or lignan ester with a cyclodextrin,
 5 wherein the lignan or lignan ester is a compound of formula (I)



or formula (II)

15



- wherein L is a lignan skeleton, which optionally includes a bridge forming a ring with one of the phenyl groups in the formulae; R₁ is H or methoxy,
 20 and R is H, methyl, R'-CO- or R'-SO₂-, wherein
 R' is a C₁ to C₂₂ alkyl, alkenyl, arylalkyl, aralkenyl, or an aromatic group, and
 R' is unsubstituted or substituted with one or more hydroxy groups and/or
 one or more carboxyl groups, an oxo group or an amino group,
 or a geometric isomer or a stereoisomer thereof, provided that R is methyl
 25 only in a single R-O- substituent in a compound of formula (I) where L is a
 skeleton of the lignan arctigenin.

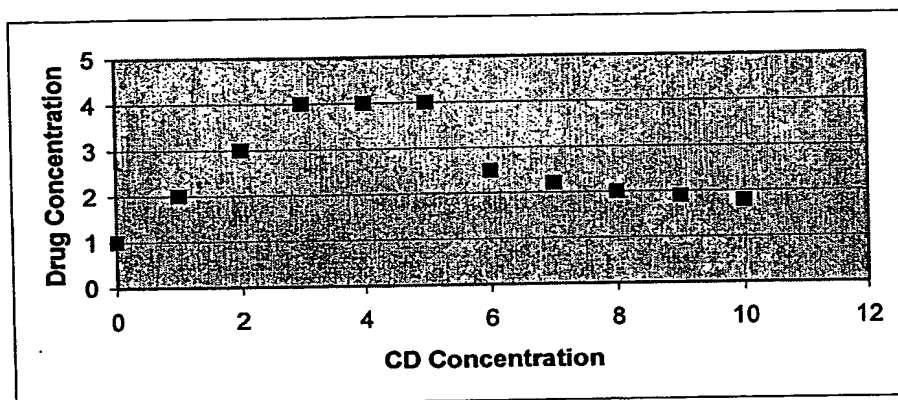
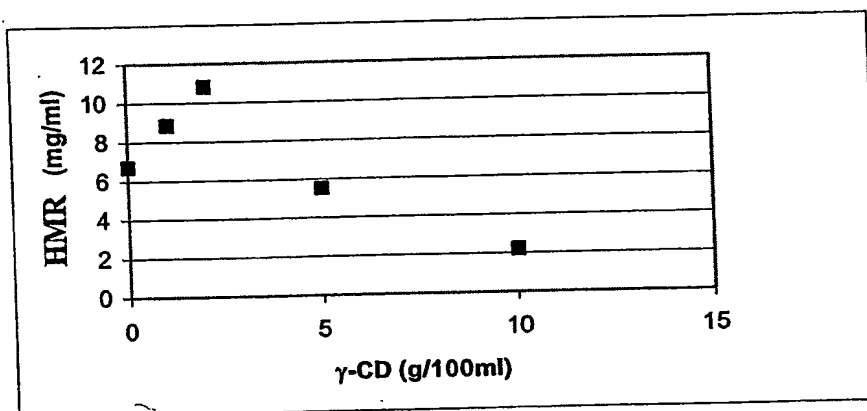
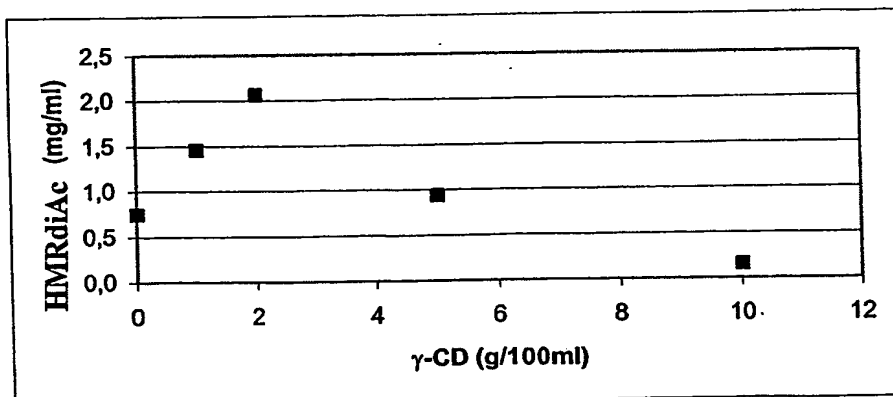
2. The complex according to claim 1 wherein the cyclodextrin is α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin or a derivative thereof.
3. The complex according to claim 2 wherein the cyclodextrin is natural
5 cyclodextrin.
4. The complex according to claim 2 wherein the cyclodextrin is γ -cyclodextrin or hydroxypropyl- β -cyclodextrin.
- 10 5. The complex according to any of the claims 1-4, wherein L in compound (I) is a lignan skeleton of any of the lignans hydroxymatairesinol, matairesinol, lariciresinol, secoisolariciresinol, isolariciresinol, oxomatairesinol, alpha-conidendrin, pinoresinol, liovil, picearesinol, arctigenin, syringaresinol or nortrachelogenin.
15
6. The complex according to any of the claims 1-4, wherein L in compound (II) is a lignan skeleton of enterolactone or enterodiol.
7. The complex according to any of the claims 1-4, wherein both of the
20 groups R-O- in the compound (I) or (II) are hydroxy groups.
8. The complex according to any of the claims 1-4, wherein both of the groups R-O- in the compound (I) or (II) are ester groups, where R is R'-CO or R'-SO₂ and R' is as defined in claim 1.
25
9. A food product comprising a complex according to any of the claims 1-8 and a foodstuff.

10. The food product according to claim 9, which is a functional food, a nutritional supplement, a nutrient, a pharmafood, a nutraceutical, a clinical nutrition product, a health food or a designer food.

5 11. A dietary supplement composition comprising a complex according to any of the claims 1-8 and an acceptable carrier.

12. A pharmaceutical composition comprising a complex according to any of the claims 1-8 and an acceptable carrier.

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**Fig. 1: B-type phase-solubility diagram****Fig. 2 Phase-solubility diagram of HMR with natural γ -CD****Fig. 3 Phase-solubility diagram of HMRdiAc with natural γ -CD**

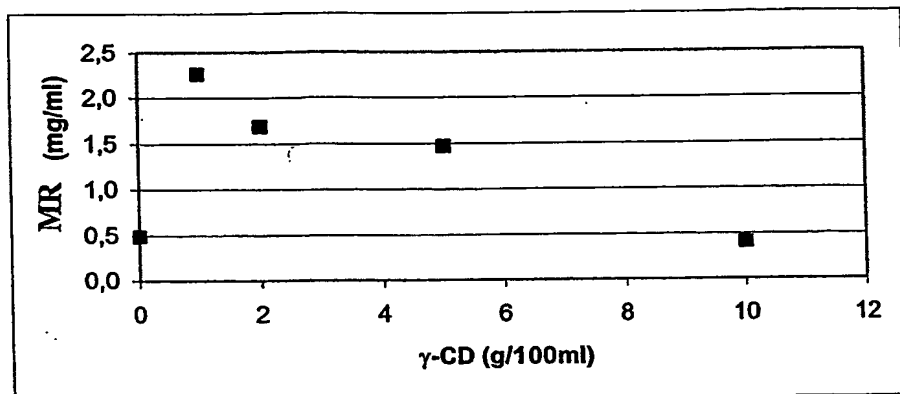


Fig. 4 Phase-solubility diagram of MR with natural γ -CD

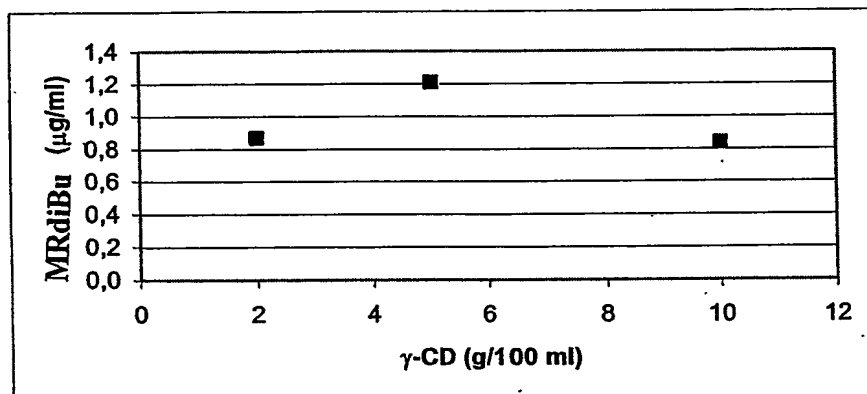


Fig. 5 Phase-solubility diagram of MRdiBu with natural γ -CD

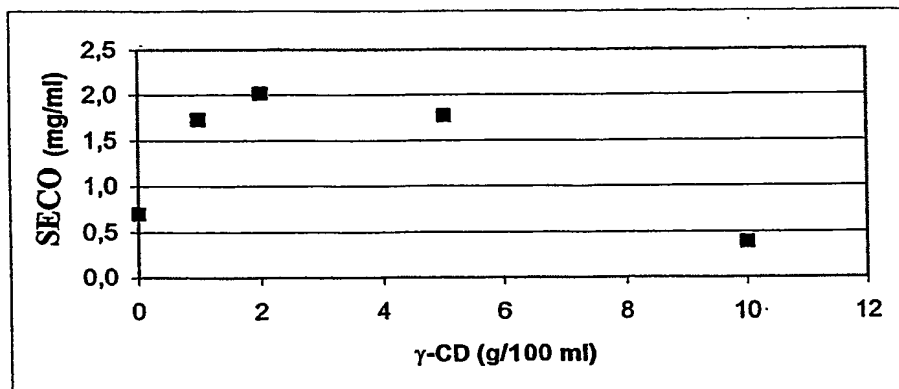


Fig. 6 Phase-solubility diagram of SECO with natural γ -CD

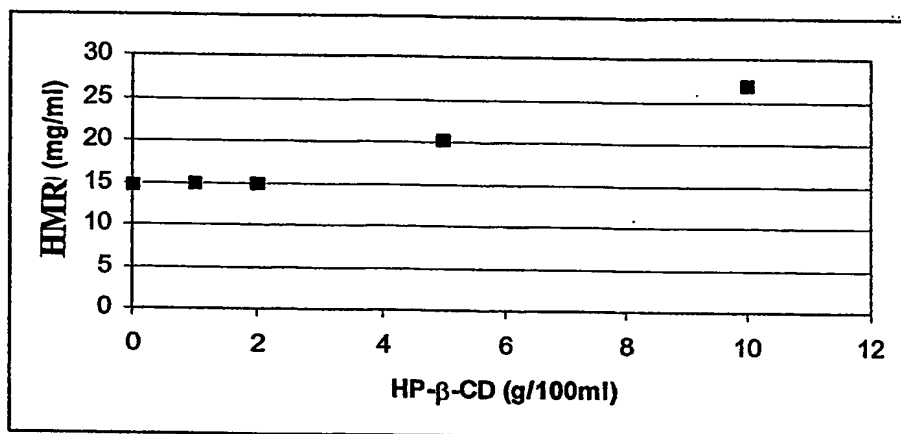


Fig. 7 Phase-solubility diagram of HMR with HP-β-CD

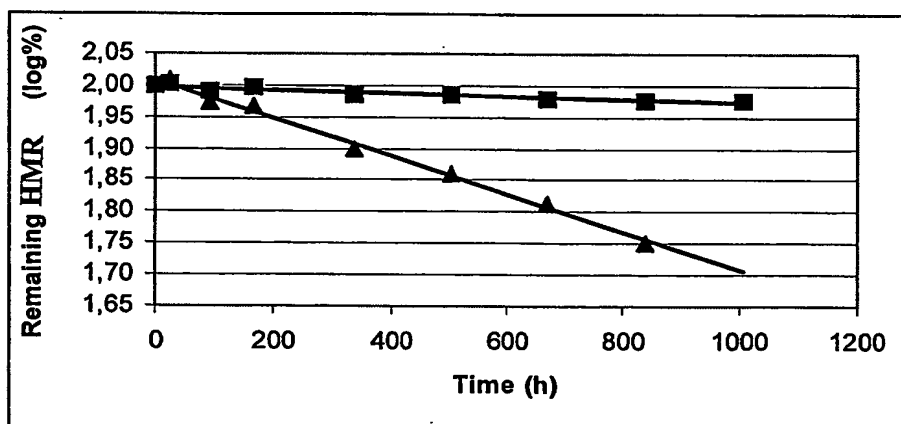


Fig. 8 First-order plots for chemical degradation of HMR in the presence (■) and absence (▲) of 2 % γ-CD at pH 5.0 (30 °C)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 03/00511

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C08B 37/16, A61K 31/724, A61K 31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C08B, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, WPI DATA, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0387000 A2 (SUNTORY LIMITED), 12 Sept 1990 (12.09.90), see page 3, lines 45-50 --	1-12
X	Il Farmaco, Volume 49, no. 1, 1994, Franco F. Vincieri et al: "Permeation of oenantie aquatica fruit tincture-beta-cyclodextrin complex through artificial membranes", page 63 - page 67 --	1-12
X	J. Nat. Prod., Volume 60, 1997, Wim Van Uden et al: The Large-Scale Isolation of Deoxypodophyllotoxin from Rhizomes of Anthriscus sylvestris Followed by Its Bioconversion into 5-Methoxypodophyllotoxin beta-D-Glucoside by Cell Cultures of Linum flavum", page 401 - page 403 -- -----	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search

23 October 2003

Date of mailing of the international search report

24-10-2003

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Information of [REDACTED] family members

International application No.

PCT/FI 03/00511

Patent document
cited in search report

Publication date

Patent family member(s)

Publication
date

EP 0387000 A2 12/09/90

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US	5336496	A	09/08/94

15/06/95

28/09/95

16/07/95

05/02/91

31/07/00

09/08/94